## REMARKS

Amendment to the Title

The title has been amended to correct the typographical errors in the spelling of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine.

Amendments to the Claims

Claim 1 has been amended to correct the typographical errors in the spelling of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine.

Claim 1 has been amended to recite "orally administering". Support for this amendment is found in the specification, for example, at page 2, lines 16-17.

Rejection of Claims 1-7 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-7 under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.*, "Effects of Acute and Chronic Administration of MCI-225, a New Selective Noradrenaline Reuptake Inhibitor with 5-$HT_3$ Receptor Blocking Action, on Extracellular Noradrenaline Levels in the Hypothalamus of Stressed Rats," *Jpn. J. Pharmacol. 83*:31-38 (2000) (hereinafter "Wu") and U.S. Patent No. 4,695,568 to Ninomiya *et al.* (hereinafter Ninomiya) in view of U.S. Patent No. 6,008,227 to Davies *et al.* (hereinafter Davies).

The Examiner stated that Wu teaches that MCI-225 is a psychoactive compound that is a selective inhibitor of noradrenaline (NA) reuptake with 5-$HT_3$-receptor blocking action reported to have antidepressant activity. Notably, the Examiner acknowledges that Wu does not teach that MCI-225 can be used to treat irritable bowel syndrome. To cure this deficiency in Wu, the Examiner relies upon the unsupported and generalized assertion in the "Background" section of Davies that monoamine uptake blockers have been useful in the treatment of chronic pain, neuralgias, migraine, sleep apnea, fibromyalgia and irritable bowel syndrome. Based on the combination of Wu and Davies, the Examiner concludes that one of ordinary skill in the art would be motivated to use MCI-225 to treat irritable bowel syndrome (functional bowel disorder). Applicants respectfully disagree for the following reasons.

*The Legal Standard*

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (2) the level of ordinary skill in the at; and (4) objective evidence of nonobviousness. *KSR*, 127 S. Ct. at 1734, 82, USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467.

The Office's examination guidelines for determining obviousness specify that after resolution of the Graham factual inquiries, the Office personnel must clearly articulate the reason why the claimed invention would have been obvious. M.P.E.P. at p 2100-119 (Rev. 6, Sept. 2007). In particular, where the Examiner's conclusion of obviousness relies on the rationale of substitution of one known element for another to obtain predictable results as in the present case, the Examiner must articulate all *four* of the following findings:

> (1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;
>
> (2) a finding that the substituted components and their functions were known in the art;
>
> (3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and
>
> (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration to explain a conclusion of obviousness.

M.P.E.P. at p. 2100-130 (Rev.6, Sept. 2007). If any of these finding cannot be made, then this rationale cannot be used to support a conclusion that the claimed subject matter would have been obvious to one of ordinary skill in the art. *Id.*

*The Present Invention*

The rejection under 35 U.S.C. § 103(a) is in error and should be withdrawn. In the present case, independent Claim 1, as amended, recites a method for the treatment of a functional bowel disorder wherein said method comprises orally administering, to a patient in need of such treatment, an effective amount of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof. The combination of Wu and Ninomiya with Davies would have failed to provide motivation to one of ordinary skill to administer MCI-225 for treating a functional bowel disorder (e.g., irritable bowel syndrome).

Wu teaches that MCI-225 is a compound having a mixed pharmacology which exhibits both inhibition of noradrenaline (NA) reuptake and blocking action of the 5-$HT_3$-receptor. The 5-$HT_3$-receptor blocking action of the MCI-225 refers to antagonism of the 5-$HT_3$-receptor, not inhibition of reuptake. Wu concludes from the studies on NA reuptake that detailed mechanisms for the pharmacological actions of MCI-225 are ***unclear***, that changes in monoamine metabolism and/or NA transport ***might*** be involved (page 37, right column) in the CNS effects of the compound and that the data suggest the ***possibility*** that MCI-225 ***might*** possess anxiolytic and/or antidepressant properties (Abstract). As such, upon reading Wu, one of ordinary skill in the art would understand that the use of MCI-225 in any indication is unpredictable, because the pharmacological actions are unclear and the effects of the drug are not established.

As noted by the Examiner, Wu does not teach that MCI-225 can be used to treat irritable bowel syndrome. As this is the case, the Examiner is relying on Davies for a teaching that monoamine reuptake blockers can be used to treat the functional bowel disorders of the presently amended claims. The specific teaching of Davies upon which the Examiner is relying is found in the "Background" section of Davies at Col. 1, line 67-Col. 2 line 2 and reads as follows: "Monoamine uptake blockers have also been useful in treatment of chronic pain, neuralgias, migraine, sleep apnea, fibromyalgia, and irritable bowel syndrome."

Applicants submit that this **one sentence** in Davies does not provide a credible teaching that any and all agents having monoamine uptake blocking action, regardless of the specific pharmacological characteristics of the agent, can be useful in the treatment of functional bowel disorders. More specifically, this **one sentence** from Davies, provides no guidance as to

pharmacological characteristics of the monoamine uptake blocker necessary to treat any of the six listed diseases. For example, there is no guidance as to:

**(a) whether specificity for blocking one class of monoamine over another is needed, depending on the indication being treated;**

**(b) whether certain classes of monoamines should be targeted for certain disorders;**

**(c) whether blocking of certain classes of monoamines should be avoided for certain disorders;**

**(d) whether the monoamine uptake blocker can have other pharmacological actions (i.e., a mixed pharmacology) and still be effective for a given indication; or**

**(e) whether the monoamine uptake blocker can lack certain pharmacological effects typically seen with monoamine uptake blockers (e.g., anticholinergic effects) and still be effective for a given indication.**

For these reasons one of ordinary skill in the art upon reading Davies would not have a reasonable expectation of success in treating functional bowel disorders with MCI-225 or any other monoamine uptake blocker.

*Davies provides no guidance as to which class of monoamine should be targeted for Applicants' claimed indication.*

According to Wu, MCI-225 inhibits noradrenaline reuptake. However, Davies does not provide any guidance as to which class of monoamines should be blocked to provide a treatment of functional bowel disorders. If one considers the teachings of Davies as a whole, it is the inhibition of the 5-HT and DA (dopamine) reuptakes which is of interest, not noradrenaline. As such, based on the teachings of Davies in combination with Wu, one or ordinary skill in the art would not be motivated to use MCI-225 to treat functional bowel disorders with any reasonable expectation of success.

*Davies teaches the need for a drug with selectivity.*

Upon reading Davies, one of ordinary skill in the art would be taught that a drug with a selective pharmacology (i.e., selective action on a specific target) is desirable. For example, Davies is trying to achieve a compound which is selective at blocking the uptake of either 5-HT or DA. Davies does not teach the need for noradrenaline reuptake blocking action (one pharmacological action of MCI-225) and therefore cannot teach the need for selectivity of this class of monoamine. In addition, the need for selectivity as taught by Davies is contrary to the use of a drug having more than one pharmacological action, such as MCI-225 with its 5-$HT_3$ receptor antagonist action. In fact, MCI-225 through its ability to antagonize the 5-$HT_3$ receptor has the capacity to indirectly exert pharmacological effects opposite to those of a 5-HT reuptake blocker. As such, one of ordinary skill in the art upon reading Davies would not be motivated to use MCI-225, because according to Wu it has a mixed, not selective, pharmacology (i.e., noradrenaline reuptake blocking and 5-$HT_3$ receptor antagonism).

*Davies does not teach or suggest that the tropane analogs described can be used to treat irritable bowel syndrome.*

A fair reading of Davies would suggest to one of ordinary skill in the art that just because a compound blocks monoamine uptake, it cannot reasonably be expected to treat functional bowel disorders (e.g., irritable bowel syndrome). For example, Davies teaches at Col. 1, lines 25-30 and Col. 3, lines 49-53, that the compounds described therein, which selectively bind either the 5-HT or DA reuptake site, have use for clinical depression, Parkinson's Disease, ADD and obesity. Notably, irritable bowel syndrome is not taught as indication for which the compounds of Davies can be used. As such, one of ordinary skill in the art upon reading Davies would not have a reasonable expectation that all monoamine uptake blockers can treat irritable bowel syndrome, because Davies does not teach the monoamine uptake blockers describe therein as useful in treating same.

In view of the above and the unpredictability in the pharmaceutical art, Applicants' claimed invention cannot be fairly stated to be obvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Provisional Rejection of Claims 1-7 Under 35 U.S.C. § 101

The Examiner has provisionally rejected Claims 1-7 under 35 U.S.C. § 101 as claiming the same invention as that of Claims 5-11 of copending Application No. 10/617,847.

*Analysis of Claims 5-11 of USSN 10/617,847*

A statutory double patenting rejection can be overcome by showing that the claims in question are not the same invention. The "same invention" means identical subject matter. Claims 5-11 are directed to a method for the treatment of a functional bowel disorder in a patient suffering therefrom, which comprises administering to the patient an effective amount of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof. In contrast, the claims of the present Application are directed to a method for the treatment of a functional bowel disorder wherein said method comprises orally administering, to a patient in need of such treatment, an effective amount of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof. The claims of the '847 Application and the claims of the present Application are not directed to the same invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. One purpose of the SIDS is to notify the Office that Dynogen Pharmaceuticals, Inc. has acquired this application from Arachnova Therapeutics, Ltd. As such, Dynogen Pharmaceuticals, Inc. now owns the instant application as well as co-pending U.S. Application Nos. 10/617,847 (also acquired), 10/757,364, 11/119,357, 11/441,905, 10/841,319, 10/841,318, 10/841,317 and 10/866,593, which are directed to similar subject matter. This information is being provided for purposes of any potential obviousness-type double patenting rejections.

Entry of the SIDS is respectfully requested. Applicants request acknowledgment of this notification by the Examiner in the next communication from the Office.

Request for Interview

Applicant would like to schedule either a telephonic or personal interview with the Examiner to discuss this application. The Examiner is requested to contact the undersigned when she is ready to act on this application.

## CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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